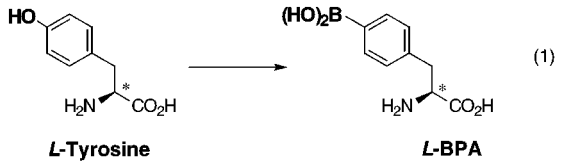
A Concise Synthesis of Enantiomerically Pure L-(4-Boronophenyl)alanine from L-Tyrosine

Hiroyuki Nakamura, Masaru Fujiwara, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Received April 30, 1998

(4-Boronophenyl)alanine (BPA)[1] is a practical boron compound, which is clinically used not only for the treatment of malignant melanoma but also for that of brain tumors, on neutron capture therapy (NCT).[1−3] Since Mishima and co-workers[4] revealed that the L-form of BPA is more efficiently incorporated into melanoma cells than the racemic one, the enantioselective synthesis of L-BPA has been required. Enriched L-BPA was prepared enzymatically through α-chymotrypsin hydrolysis[5] of the ethyl ester of racemic BPA synthesized by the traditional method.[1,6] In this case, 50% of another enantiomer (D-BPA) was recovered from the racemic material. Recently, two synthetic routes of L-BPA were reported. An asymmetric hydrogenation route gave L-BPA with enantiomeric excess of up to 88% (96% ee after recrystallization).[7] Another route using palladium-catalyzed coupling reaction of (iodophenyl)boronate with the chiral organozinc derived from L-serine needed rather lengthy synthetic steps.[8] Herein we report a concise synthesis of enantiomerically pure L-BPA from L-tyrosine using palladium-catalyzed carbon−boron bond formation reaction (eq 1).

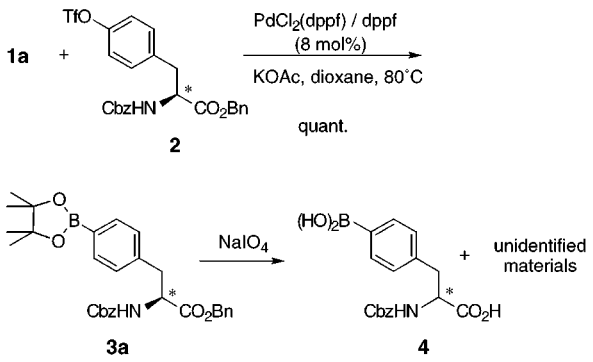


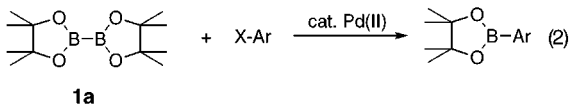
L-Tyrosine *L*-BPA (1)

Results and Discussion

Palladium-catalyzed cross-coupling reaction of the pinacol ester of diboronic acid **1a** with haloarenes, which was developed by Miyaura, is a direct procedure for the synthesis of arylboronic esters from haloarenes (eq 2).[9]

Scheme 1





Triflate **2** was readily prepared from L-tyrosine by the literature procedure.[10] The cross-coupling reaction of the triflate **2** with **1a** in dioxane proceeded very smoothly in a catalytic amount of $PdCl_2$(dppf) (1,1′-bis(diphenylphosphino)ferrocene), giving the corresponding arylboronic ester **3a** in quantitative yield. However, subsequent hydrolysis of pinacol ester **3a** with $NaIO_4$[11] gave an unseparable mixture of the boronic acid **4** and unidentified materials[12] (Scheme 1). The removal of the Cbz (carbobenzoxy) protecting group by the treatment of **4** with either Pd catalyst/H_2 or acidic reagents gave a mixture of the desired product (L-BPA) and unidentified materials, and separation of L-BPA from the mixture was difficult. The other hydrolysis method, based on transesterification with phenylboronic acid, was not effective for arylboronic ester **3a**.[11]

Thus, 1,3-diphenyl-1,3-propanediol (**5**) was chosen as an ester group of diboron since the boronic ester derived

(1) Snyder, H. R.; Reedy, A. J.; Lennarz, W. M. J. *J. Am. Chem. Soc.* **1958**, *80*, 835.

(2) (a) Locher, G. L. *Am. J. Roentgenol.* **1936**, *36*, 1. For recent reviews, see: (b) Hawthorn, M. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 950. (c) Yamamoto, Y. *Pure Appl. Chem.* **1991**, *63*, 423. (d) Barth, R. F.; Soloway, A. H.; Fairchild, R. G. *Cancer Res.* **1990**, *50*, 1061. (e) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Wyzlic, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515.

(3) For our recent papers on NCT, see: (a) Yamamoto, Y.; Seko, T.; Nakamura, H.; Nemoto, H.; Hojo, H.; Mukai, N.; Hashimoto, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 157. (b) Yamamoto, Y.; Seko, T.; Nakamura H.; Nemoto, H. *Heteroatom Chem.* **1992,** *3*, 239. (c) Nemoto, H.; Wilson, J. G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 435. (d) Yamamoto, Y.; Nakamura, H. *J. Med. Chem.* **1993**, *36*, 2232. (e) Yamamoto, Y.; Takamatsu, S.; Nakamura, H. *J. Magn. Reson. Ser. B* **1993**, *101*, 198. (f) Nemoto, H.; Cai, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994,** 577. (g) Nakamura, H.; Sadayori, N.; Sekido, M.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2581. (h) Nemoto, H.; Cai, J.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 539. (i) Nakamura, H.; Sekido, M.; Yamamoto, Y. *J. Med. Chem.* **1997**, *40*, 2825.

(4) (a) Mishima, Y.; Honda, C.; Ichihashi, M.; Obara, H.; Hiratsuka, J.; Fukuda, H.; Karashima, H.; Kobayashi, T.; Kanda, K.; Yoshino, K. *Lancet* **1989**, 388. (b) Mishima, Y.; Ichihashi, M.; Hatta, S.; Honda, C.; Yamamura, K.; Nakagawa, T. *Pigm. Cell Res.* **1989**, *5*, 226.

(5) Roberts, D. C.; Suda, K.; Samanen, J.; Kemp, D. S. *Tetrahedron Lett.* **1980**, *21*, 3435.

(6) Kirihata, M.; Morimoto, T.; Ichimoto, I. *Biosci. Biotech. Biochem.* **1993**, *57*, 1940.

(7) Samsel, E. G. U.S. Patent 5157149, 1992; *Chem. Abstr.* **1993**, *118*, 125073.

(8) Malan, C.; Morin, C. *Synlett* **1996**, 167.

(9) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457 and references therein.

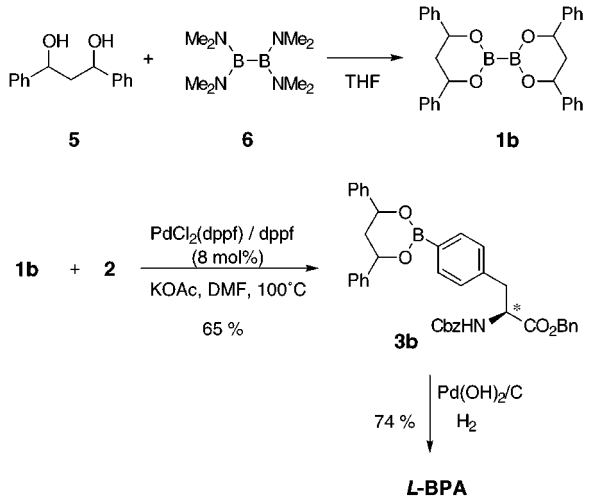
(10) Wang, W.; Obeyesekere, N. U.; McMurray, J. S. *Tetrahedron Lett.* **1996**, *37*, 6661.

(11) Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. *Tetrahedron Lett.* **1994**, *35*, 5109.

(12) Arylboronic ester **3a** showed an optical rotation of $[\alpha]_D^{22.4}$ +6.53 (c = 1.0, $CHCl_3$). The unseparable mixture of the boronic acid **4** and unidentified materials showed an optical rotation of $[\alpha]_D^{25}$ −0.7 (c = 0.96, CH_3OH). Treatment of this mixture with pinacol followed by the esterification with benzyl bromide/Cs_2CO_3 gave **3a**, which showed $[\alpha]_D^{24.5}$ +6.65 (c = 1.90, $CHCl_3$). This clearly indicates that no racemization has taken place at the stage of deprotection of pinacol and benzyl groups.

S0022-3263(98)00818-4 CCC: $15.00
Published on Web 09/19/1998

Scheme 2



from this diol can be easily cleaved by hydrogenolysis.[13] The reaction of the diol **5** and tetrakis(dimethylamino)-diboron (**6**)[14] proceeded very smoothly in THF at room temperature to give bis(1,3-diphenyl-1,3-propanediolato)-diboron (**1b**) in 72% yield (Scheme 2). The triflate **2** underwent the palladium-catalyzed cross-coupling reaction with the diboron **1b** in DMF at 100 °C, giving the corresponding arylboronic ester **3b** in 65% yield. The use of dioxane as a solvent gave **3b** in lower yield. The protective groups of **3b** were removed all at once under the hydrogenolytic condition with $Pd(OH)_2/C$, and L-BPA was obtained in 74% yield without racemization.

The palladium-catalyzed cross-coupling reaction between C−OTf and B−B bonding is a key for the concise synthesis of L-BPA from L-tyrosine. We are now in a position to supply L-BPA, synthesized through short steps from naturally occurring L-tyrosine, for medical and biological research.

Experimental Section

Cbz-Tyr-OBzl. To a solution of L-tyrosine (10 g, 55 mmol) and benzyl alcohol (25 mL) in benzene (120 mL) was added $TsOH·H_2O$ (12.6 g, 66 mmol) at room temperature. The water generated in the reaction was separated by benzene azeotropic distillation for 2 h, and the white precipitate was filtered off. The filtrate was washed with $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. Purification by recrystallization from ethanol gave Tyr-OBzl (11.9 g). To a solution of Tyr-OBzl (11.9 g, 44 mmol) and triethylamine (6.2 mL, 44 mmol) in methanol (200 mL) was slowly added carbobenzoxy chloride (Cbz-Cl) (6.1 mL, 44 mmol) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched with water, and the mixture was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (3:1 hexane/ethyl acetate) gave Cbz-Tyr-OBzl (16.5 g, 73% yield from L-tyrosine) as a white solid: IR (KBr) 3422, 3314, 1724, 1693, 1252, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 10H), 6.83 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 5.58 (br, 1H), 5.27 (d, J = 8.5 Hz, 1H), 5.14 (m, 2H), 5.09 (s, 2H), 4.67 (m, 1H), 3.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 155.8, 154.9, 136.1, 135.0, 130.4, 128.6, 128.58, 128.5, 128.5, 128.2, 128.1, 115.5, 67.3, 67.1, 55.0, 37.3; HRMS (EI) calcd for $C_{24}H_{23}NO_5$ m/z 405.1576, found m/z 405.1585. Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.14; H, 5.76; N, 3.46.

Bis(1,3-diphenyl-1,3-propanediolato)diboron (1b). To a solution of tetrakis(dimethylamino)diboron (**6**) (3.16 g, 16.0 mmol) in THF (40 mL) was added 1,3-diphenyl-1,3-propanediol (**5**) (7.30 g, 32.0 mmol) at room temperature, and the mixture was stirred overnight at 50 °C. The solvent was removed, and the resulting crude product was purified by recrystallization from THF to afford **1b** as a white solid (5.43 g, 72% yield): IR (KBr) 3084, 3030, 2903, 1385, 1277, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 20H), 5.08 (t, J = 5.3 Hz, 4H), 2.36 (dd, J = 5.3, 5.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 128.4, 127.4, 125.2, 69.8, 41.8; HRMS (EI) calcd for $C_{30}H_{28}O_4B_2$ m/z 474.2174, found m/z 474.2171. Anal. Calcd for $C_{30}H_{28}O_4B_2$: C, 75.99; H, 5.95. Found: C, 75.96; H, 6.10.

Cbz-Tyr(Tf)-OBzl (2). To a solution of Cbz-Tyr-OBzl (2.3 g, 5.7 mmol) and 2,6-lutidine (2.7 mL, 22.6 mmol) in CH_2Cl_2 (30 mL) was added triflic anhydride (1.9 mL, 11.3 mmol) at −40 °C and the mixture was stirred for 2 h. The reaction was quenched with water and the organic portion was extracted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (5:1 hexane/ethyl acetate) gave Cbz-Tyr(Tf)-OBzl (**2**) (2.48 g, 83% yield) as white solid: IR (KBr) 3342, 1744, 1693, 1541, 1417, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 9H), 7.02 (s, 5H), 5.25 (d, J = 8.0 Hz, 1H), 5.07 (s, 4H), 4.68 (m, 1H), 3.14 (dd, J = 13.2, 5.6 Hz, 1H), 3.05 (dd, J = 13.2 5.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.4, 148.4, 136.2, 136.0, 134.7, 131.1, 128.8, 128.7, 128.7, 128.5, 128.3, 128.1, 121.2, 121.0, 67.5, 67.1, 54.6, 37.4; HRMS (EI) calcd for $C_{25}H_{22}NO_7SF_3$ m/z 537.1069, found m/z 537.1068. Anal. Calcd for $C_{25}H_{22}NO_7SF_3$: C, 55.86; H, 4.13; N, 2.61. Found: C, 55.73; H, 4.04; N, 2.75. $[\alpha]_D^{20.9}$: +2.87 (c = 1.055, $CHCl_3$).

(*S*)-Benzyl 2-((Benzyloxycarbonyl)amino)-3-[4-(((1,3-diphenyl-1,3-propanediyl)dioxo)diolatoborio)phenyl]-propanoate (3b). A solution of Cbz-Tyr(Tf)-OBzl (**2**) (1.34 g, 2.49 mmol), bis(1,3-diphenyl-1,3-propanediolato)diboron (**1b**) (1.30 g, 2.74 mmol), KOAc (0.73 g, 7.48 mmol), $PdCl_2$(dppf) (0.15 g, 0.20 mmol), and dppf (0.11 g, 0.20 mmol) in DMF (20 mL) was stirred at 100 °C under argon atmosphere for 3 h. The reaction mixture was diluted with ether, washed with NaCl solution, dried over $MgSO_4$, and concentrated. Purification by column chromatography on silica gel (6:1 hexane/ethyl acetate) gave **3b** (1.04 g, 65% yield) as a white solid: IR (KBr) 3420, 3339, 1703, 1497, 1456, 1312, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.3 Hz, 2H), 7.36 (m, 20H), 7.08 (d, J = 7.3 Hz, 2H), 5.25 (m, 1H), 5.21 (t, J = 5.20 Hz, 2H), 5.15 (s, 2H), 5.10 (s, 2H), 4.75 (m, 1H), 3.15 (br, 2H), 2.40 (dd, J = 5.2, 5.2 Hz, 2H); HRMS (EI) Calcd for $C_{39}H_{36}BNO_6$ m/z 625.2636, found m/z 625.2667. Anal. Calcd for $C_{39}H_{36}BNO_6$: C, 74.89; H, 5.80; N, 2.24. Found: C, 74.92; H, 6.02; N, 2.35. $[\alpha]_D^{21.2}$: +10.13 (c = 0.235, $CHCl_3$).

L-(4-Boronophenyl)alanine (L-BPA). To a mixture of **3b** (0.38 g, 0.59 mmol) and $Pd(OH)_2/C$ (0.10 g) in $CHCl_3$−MeOH (1:1) solution was added 1 drop of AcOH under hydrogen atmosphere, and the reaction mixture was stirred at 40 °C for 24 h. Palladium catalyst was removed by filtration through Celite, and the solvent was evaporated. The white solid was washed with CH_2Cl_2 to afford pure *L*-BPA (0.09 g, 74% yield): ^1H NMR (300 MHz, DCl + D_2O) δ 7.61 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.7 Hz, 2H), 4.11 (bt, J = 6.8 Hz, 1H), 3.21 (dd, J = 14.5, 5.5 Hz, 1H), 3.06 (dd, J = 14.5, 7.7 Hz, 1H); $[\alpha]_D^{21.3}$ −8.12 (c = 0.8, 1 N HCl); lit.[5] $[\alpha]_D^{23}$ −8.2 (c = 0.7, 1 N HCl).

Acknowledgment. We thank Professor Norio Miyaura of Hokkaido University for his helpful advice on the synthesis of the diboron compounds and their palladium-catalyzed coupling reaction and Professor Yuzuru Masuda of Kitami Institute of Technology for his helpful discussions.

JO980818R

(13) Malan, C.; Morin, C.; Preckher, G. *Tetrahedron Lett.* **1996**, *37*, 6705.

(14) Brotherton, R. J.; McCloskey, A. L.; Petterson, L. L.; Steinberg, H. *J. Am. Chem. Soc.* **1960**, *82*, 6242.